Valuing the health states associated with *Chlamydia trachomatis* infections and their sequelae: a systematic review of economic evaluations and primary studies.

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Authors:

Louise J. Jackson (PhD)[a], Peter Auguste (MSc)[b], Nicola Low (MD, FFPH)[c] and Tracy E. Roberts (PhD) [a]*

[a] Health Economics Unit, University of Birmingham, UK

[b] Warwick Evidence, Warwick Medical School, The University of Warwick, Coventry, UK

[c] Institute of Social and Preventive Medicine, University of Bern, Switzerland

*Corresponding author

Abstract

Objectives: Economic evaluations of interventions to prevent and control sexually transmitted infections (STIs) such as *Chlamydia trachomatis* are increasingly required to present their outcomes in terms of Quality Adjusted Life Years (QALYs) using preference-based measurements of relevant health states. The objectives of this study were to critically evaluate how published cost effectiveness studies have conceptualised and valued health states associated with chlamydia and to examine the primary evidence available to inform health state utility values (HSUVs).

Methods: A systematic review was conducted, with searches of six electronic databases up to December 2012. Data on study characteristics, methods and main results were extracted using a standard template.

Results: Nineteen economic evaluations of relevant interventions were included. Individual studies considered different health states and assigned different values and durations. Eleven studies cited the same source for HSUVs. Only five primary studies valued relevant health states. The methods and viewpoints adopted varied, and different values for health states were generated.

Conclusions: Limitations in the information available about HSUVs associated with chlamydia and its complications have implications for the robustness of economic evaluations in this area. None of the primary studies could be used without reservation to inform cost-effectiveness analyses in the UK. Future debate should consider appropriate methods for valuing health states for infectious diseases, as recommended approaches may not be suitable. Unless we adequately tackle the challenges associated with measuring and valuing HRQL for chlamydia and other infectious diseases, evaluating the cost-effectiveness of interventions in this area will remain problematic.

Introduction

Evidence about the cost-effectiveness of health care interventions is an integral requirement for key decision making bodies in many countries, including the UK (1, 2). Many decision making bodies require interventions to be assessed in terms of their cost per Quality Adjusted Life Year (QALY), which combines improvements in health-related quality of life and life expectancy, together with people's relative preferences for health states (3). Preference- based health state utility values (HSUVs) assign a value to the health states experienced by the patient. A value of 'one' represents full health and 'zero' indicates a health state equivalent to being dead. Utility values can be generated directly or indirectly. Standard gamble (SG) or time trade off (TTO) techniques generate direct valuations from patients or the public, based on their experiences or hypothetical scenarios. Indirect methods typically use an instrument to measure health related quality of life (HRQL) and then apply preference values obtained from surveys of the general public (4). The conceptualisation of health states and application of HSUVs can have a major influence on the results of cost-effectiveness studies (5, 6). There is a growing body of literature with estimates for HSUVs for a wide range of conditions which can be used to inform cost-effectiveness studies when reliance on primary data is not possible or valid (7). However, there are many disease areas where HSUVs are less widely available, and there are subsets of populations for whom preference-based measurements of HRQL are less well researched or where such measurement is perceived as more difficult (8, 9).

Cost-effectiveness studies influence decisions about funding for particular interventions, so their methodological quality is extremely important (10). While there has been a growing literature aimed at improving the standard of economic evaluations and the decision-analytic models which inform them, less attention has been devoted to the methods involved in identifying and applying HSUVs (6, 11). The conceptualisation and structure of a decision-analytic model determines how health states are defined and represented, so disease processes must be represented appropriately (12).

As with all model input parameters estimated from secondary sources, a systematic review of the literature should be done to identify, assess and synthesise information to estimate HSUVs and uncertainty needs to be fully reported and examined (11, 13, 14). Two sets of criteria are relevant to the assessment and selection of HSUVs (5). The first relates to the descriptive systems, methods and sources used to generate the values; in the UK these are likely to be assessed against recommendations from the National Institute for Health and Care Excellence (NICE) (15, 16). The second relates to the relevance of the population in the utility study to that in the economic evaluation, in terms of factors such as the condition, its severity, and patients' age profiles.

Many investigators have studied the cost-effectiveness of interventions to prevent, control and treat *Chlamydia trachomatis* (17-19). Chlamydia is the most common bacterial sexually transmitted infection (STI) worldwide (20) and in the UK (21), with an estimated prevalence in sexually active 15-25 year olds in the general population of 3-6% (22-24). Chlamydia first infects the lower genital tract, causing cervicitis in women and urethritis in men, both of which are usually asymptomatic (25) and last more than a year, on average, if untreated (26). Infection can clear spontaneously or can ascend to the upper genital tract at any time (27), causing symptoms of pelvic inflammatory disease (PID) in 10-15% of women (28, 29) and epididymo-orchitis in a smaller proportion of men (25). Symptoms of PID include lower abdominal pain and pain during sexual intercourse. Fallopian tube inflammation can, rarely, cause tubo-ovarian abscess. Tubal scarring and blockage can cause chronic pelvic pain, ectopic pregnancy and tubal factor infertility (30). There is uncertainty about the incidence, duration and timing of late complications because contraception can delay their diagnosis for many years and chlamydia is only one cause (31). Chlamydial infection during pregnancy is associated with premature labour and neonatal infection can cause conjunctivitis and pneumonia (32, 33).

Screening for chlamydia infection in asymptomatic sexually active young adults is recommended because of the frequency of asymptomatic infections, the severity of complications, and the easy availability of both reliable diagnostic tests and efficacious antibiotic treatment. If decision makers are to interpret cost-effectiveness analyses of interventions to prevent and control chlamydia appropriately, their HSUVs must reflect the impact on those experiencing complications.

The challenges associated with valuing health states for chlamydia

We believe that there are several challenges to the identification, assessment and utilisation of appropriate information on HSUVs for use in economic evaluations of STIs such as chlamydia. First, there are considerations relating to the actual state of infection itself. Chlamydia, like many STIs, is often asymptomatic, so most infected individuals do not experience any apparent detriment to their quality of life at the time of infection (34), even though the average duration of untreated infection is more than one year and people are infectious throughout (26). There is qualitative evidence, however, to suggest that being tested for chlamydia and receiving a positive diagnosis does have an impact on quality of life, particularly for women (35, 36). Second, owing to the obvious ethical and practical issues associated with studying untreated chlamydia, there is considerable uncertainty about the natural history of infection and disease, including the timing, incidence and duration of complications (37, 38) and rates and risks associated with reinfection (31).

Third, chlamydia is only one cause of many of the late sequelae associated with the infection. There is limited evidence about whether the aetiology of conditions such as chronic pelvic pain or infertility affects HRQL (39-41). Qualitative evidence suggests that the stigma associated with STIs mediates the experience of being in the health state (35) so HRQL might differ between women with infertility secondary to an STI and those with cancer, for example. Fourth, the health states associated with chlamydial disease last for different amounts of time; tubal infertility might be permanent, whilst the infection itself and some of its sequelae, such as PID and ectopic pregnancy are temporary states (42, 43). Temporary health states might involve different methods for valuation, and there is a need to consider how preferences for temporary and permanent states are combined (44). Fifth, the sequelae associated with chlamydia sometimes occur many years after the initial infection (37), so issues of time preference are likely to impact on the valuation of the health states (45, 46). Finally, the burdens associated with the disease are asymmetrical; although both men and women experience infection, the main complications associated with chlamydia affect women of reproductive age (31), but fertility problems can affect others besides the woman herself. This might affect the conceptualisation of health outcomes and decisions about whose preferences should count (47, 48).

The objectives of this study were to identify and critically evaluate economic evaluations that included QALYs as an outcome measure to identify how health states have been conceptualised and valued within cost-effectiveness studies. Primary studies which valued relevant health states were also located, to examine the data which could be used to inform cost-effectiveness studies incorporating HSUVs for chlamydia and its sequelae.

Methods

We conducted a systematic review following UK Centre for Review and Dissemination (CRD) guidelines for methods and PRISMA guidelines for reporting, where appropriate (49, 50).

Inclusion criteria

Papers were included if they met the following criteria: the participants were men or women with, or at risk of, sexually transmitted chlamydia or its sequelae; the intervention (for economic evaluations) was any medical procedure to prevent, control or treat chlamydia infection or its sequelae; the main outcomes were either cost per QALY (for economic evaluations), or the measurement and valuation of health states associated with chlamydial infection and its sequelae. We excluded papers which were wholly concerned with conditions affecting the pelvic area and not likely to be connected with STIs.

Search strategy

The search strategy was constructed to be as inclusive as possible. Six electronic databases were searched (EMBASE, MEDLINE, Web of Science, NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA)) up to December 2012 (Appendix 1). The reference lists of potentially relevant papers were then hand searched to identify additional studies. We used a three stage process to identify studies for inclusion, using methods which have been described in detail elsewhere (51). Two reviewers initially screened papers using the title and abstract to classify them into five groups (A to E) (Appendix 2). Second, two reviewers read the full texts of potentially relevant studies and further classified them (Appendix 2, as above). Quality assessment criteria were not applied to exclude studies because so few were identified. For each included study, one reviewer extracted data about the study characteristics, the characteristics of the participants, the health states examined, the methods and instrument(s) used and the results reported and a second reviewer checked the data. The data were tabulated and the findings of individual studies were compared narratively.

Results

The electronic database search identified 6383 published papers, of which 2001 were duplicates. Figure 1 shows a flow diagram of the papers identified, retrieved and retained or excluded at each stage, and the categorisation of the articles.

Nineteen economic evaluations using QALYs were identified and all were included for data extraction. There were 58 papers which incorporated descriptive measurement of HRQL for chlamydia and associated conditions but only five which included preference-based measurement of such health states.

Economic evaluations using cost per QALY

Table 1 summarises the characteristics of the 19 studies. Four studies included individuals who were considered to be at high risk of STIs (52-55). Ten articles examined interventions to provide chlamydia or gonorrhoea screening (52-54, 56-62), while two articles examined different aspects of interventions to treat or prevent PID (63, 64). Two studies focused on behavioural interventions (55, 65), and one examined a multifaceted intervention to provide information and increased availability of testing and treatment (66). One article was concerned with the overall costs and 'burden of disease' for chlamydia in a particular country (67) and another aimed to estimate the lifetime cost of PID (68). Two studies examined the impact of expedited treatment for sexual partners of people with an STI and the impact of contraceptive use on STI prevention (69, 70). Fifteen

studies presented their results in terms of natural units, e.g. cost per adverse outcome avoided, as well as cost per QALY.

Authors of five studies applied HSUVs for uncomplicated chlamydia infection, including cervicitis and urethritis (52, 54, 60, 61, 66). Most applied HSUVs for one or more named female reproductive tract complications: PID (52, 54, 56, 59-67, 69, 70); ectopic pregnancy (54, 56, 57, 59-66, 70); tubal factor infertility (54,56,57,59-66, 68) and chronic pelvic pain (54,57,60-66,68). Fewer studies considered male complications (54, 56, 59, 65-67) or neonatal complications (56, 59, 66). Just over half of the studies used HSUVs provided by a study by the Institute of Medicine in the United States (US) (52, 56-58, 60-64, 66, 68) although some did not cite the study directly. Of the remaining evaluations, two studies (59,69) used values elicited from women with PID from the work of Smith et al. (71) and one study used the same source but employed values elicited from women without PID (67). For one cost-effectiveness study the source of the utility values was unclear (55) and the authors of one economic evaluation used a convenience sample to generate their own utility values (70).

Although the economic evaluations identified largely relied on the same source for HSUVs, there were differences in the actual values used, the duration over which they were applied, and around the assumed timing and incidence of sequelae (Table 2). The base case values used for chronic pelvic pain varied between 0.6 (57, 60-64, 66, 68) and 0.79 (67) and were applied for durations from 5 years (54, 60-62, 65) to the rest of the woman's life (67). For ectopic pregnancy, the values adopted varied between 0.58 (60-64, 66) and 1 (57). For infertility, the utilities included varied between 0.76 (65) and 0.87 (59). Most analysed the uncertainty associated with such values in sensitivity analyses (52, 54-57, 59-70), and some found that this had an impact on the results of the cost-effectiveness analysis (63, 65, 68), although factors such as complication and transmission rates were more important. The majority of the studies did not provide information about the utility values they adopted (other than the source) and very few discussed their appropriateness for the population under study. About half of the studies acknowledged the lack of information regarding HSUVs, for example in relation to the limitations associated with their study (56, 59-62, 65, 67, 68, 70) (Table 1).

Primary studies providing HSUVs for relevant health states

Five primary studies valued HRQL for health states relevant to chlamydia. Their aims and characteristics are shown in Table 3; all were based in the US. The studies provided valuations for a range of relevant health states including PID, chronic pelvic pain, ectopic pregnancy and tubal factor infertility.

Pelvic inflammatory disease (PID)

Three studies generated utility values for PID (71-73). The values obtained for PID treatment (Table 4) are difficult to compare between studies because each study made different assumptions about treatment pathways (e.g. inpatient and outpatient care). Two of these measured both public and patient preferences. Smith et al. included valuations from women with a history of PID and women with no experience of this condition (71). Trent et al. compared the utilities for health states obtained directly from adolescents (assumed to give an indication of the views of patients) and their parents (assumed to represent the views of the public) (72). One study provided preferences from the perspective of the public using indirect methods. The study conducted by the US Institute of Medicine used experts to measure HRQL using the HUI-2 and then used the tariffs associated with this instrument for valuation, which are based on surveys of the general population (73). Smith et al. used Visual Analogue Scale (VAS) and TTO techniques with a 10 year time horizon to value all health states directly and Trent et al. employed VAS and TTO techniques with a 50 year time period (71, 72). The health states in the US Institute of Medicine study were not described in full but different time horizons were used for different conditions (73).

Ectopic pregnancy

Utility values for ectopic pregnancy were generated in three studies (71-73) using the methods and participants described above. As for PID, the utility values (Table 4) could not be directly compared between studies due to differing assumptions made about treatment pathways. The highest utility value for this condition was generated by parents of adolescents for a scenario involving a 15 year old girl experiencing pain and possibly requiring an operation with the condition resolved in a few weeks (0.9) (72). The lowest value was generated for inpatient treatment for ectopic pregnancy using the HUI-2 (0.23, with an expected duration of 3 days), which was followed by outpatient treatment (0.66 for 4 weeks) (73).

Tubal factor infertility

Four of the primary studies provided utility vales for tubal factor infertility. Two studies used similar scenarios to generate values directly, but with different participants and time horizons. Smith and colleagues reported lower utility values for women with experience of PID (0.76) compared with women with no experience of PID (0.84), while Trent et al reported similar values for adolescents (0.84) and higher values for their parents (0.91) (71, 72). The Institute of Medicine's study reported a utility value of 0.82 using the HUI-2 tool; infertility was assumed to last for the woman's remaining lifetime (73). Songer et al. used a scaling method to compare

preferences for infertility against a range of chronic conditions as they felt that TTO techniques were not suitable for eliciting the preferences associated with infertility (75). The authors reported that infertility was viewed as worse than a chronic headache by 48% of participants and as worse than paralysis by 12%. There were differences in preferences based on experience of previous pregnancies and the number of children respondents had.

Chronic pelvic pain

Utility values for chronic pelvic pain were reported by four of the studies. Kuppermann et al. obtained preference values using Time Trade Off (TTO) techniques with the patients in their cross-sectional study of women seeking care for non-cancerous pelvic problems (74). The women generated a utility value of 0.83 for their pain, based on living for the rest of their lives with their current symptoms. Smith et al. also provided values from a patient perspective; women with experience of PID generated a value of 0.69 for pelvic pain, compared with a value of 0.79 provided by women without experience of PID (71). The description of the health state used by Smith and colleagues was slightly different to that adopted in the study by Kupperman et al. as it was stated that the pain may go away. Trent and colleagues used a similar scenario to that of Smith et al, but the subject was a 15 year old girl and 50 year time horizon was used within the TTO exercise. While adolescents gave a value of 0.76 for this health state, their parents reported a slightly higher value of 0.85 (72). The study by the Institute of Medicine generated a HUI-2 value of 0.60, and the condition was assumed to last for the remainder of the woman's life (73).

Discussion

This systematic review found 19 published economic evaluations about chlamydia infection and associated sequelae that reported outcomes as cost per QALY. Half of the articles used the same source for HSUVs but several applied modified values or altered the duration for which they were applied. Half of the economic evaluations mentioned some difficulties associated with valuing the health states for chlamydia. Most studies analysed the uncertainty around HSUV estimates for the state of infection and its sequelae through a sensitivity analysis but none discussed in detail the implications associated with the primary research informing their HSUV estimates. There were five primary studies that provided HSUVs for health states relevant to chlamydia infection; all but one used direct methods to value health states.

As for many infectious diseases, understanding the impacts of chlamydia upon HRQL involves assessing the nature and epidemiology of the sequelae and our ability to link them back to infection. In the majority of the economic evaluations limitations around our understanding of HRQL for the health states associated with chlamydia and its sequelae were not fully explored and the ways in which health states had been conceptualised and valued were not discussed in detail. For example, the primary studies demonstrated that health states were valued very differently depending on the characteristics of the research participants (e.g. patients or public), but the economic evaluations reviewed did not discuss the implications associated with the values they adopted. In economic evaluations of diseases where the primary evidence is limited, balancing the need to adequately reflect the decision problem and disease processes against the availability and quality of data can be problematic (12). While the economic evaluations have clearly attempted to tackle the complexities involved in understanding the impacts of interventions in this area, we believe that it is imperative that such studies fully convey the limitations in our knowledge about the sequelae of chlamydia and about preference-based HRQL for these conditions, to ensure that decision makers are fully informed and to emphasise the importance of further primary research to inform such economic analyses.

None of utility values reported in the primary studies we identified could be used without reservation to inform economic evaluations in the UK. When selecting HSUVs from the literature, it is important to consider both the methods used to generate the values and their relevance to the population under consideration (4). In this instance, the methods used in the primary studies would need to be considered against the 'reference case' methods for estimating cost-effectiveness set out by NICE, which recommends that, where possible, HRQL is measured directly by patients or their carers and that these measurements are valued by a representative sample of the general population using a choice based method (15). The study by the Institute of Medicine relied on expert views to measure HRQL, which is generally seen as less preferable than measuring patient experiences of health states directly (4). The remaining studies employed scenarios to value HRQL rather than direct patient measurement. There might also be some concerns about the generalisability of the studies. The study by Kupperman et al. provided values based on the specific symptoms the women with pelvic problems were experiencing, and the studies by Smith et al. and Trent et al. were carried out in areas of high STI prevalence in the US, which would not apply to the UK general population.

Infectious diseases and their sequelae offer an intriguing lens through which to analyse methodological debates about how we should measure and value the benefits of health care; enabling exploration of key questions such

as how should HRQL be described and measured, how should it be valued and whose values should be taken into account (5). For chlamydia, it is difficult to measure patient reported HRQL directly because sequelae can happen a long time after the initial infection and cannot be aetiologically linked. This means that most primary studies to date have employed direct valuation methods using descriptions of health states. However, direct valuation methods are seen as less robust, as there is no clear link to patient reported HRQL (4). For conditions where it is difficult to measure preferences indirectly, there is a need for further discussion about the most effective ways to elicit utility values to inform economic evaluations (76). There is a growing body of research examining the impacts of stigma on HRQL in relation to STIs and other conditions (77-80) and there have been attempts to include the impacts of stigma in the valuation of health states (81), but further exploration of such issues is needed.

Infectious diseases such as chlamydia involve combinations of short and long-term health states. There is evidence that preferences for health states may be partly affected by their duration and there is on-going debate about how we overcome such problems (44, 82). There is also discussion about how we incorporate time preference within valuations of health states, which is pertinent to research involving chlamydia and other diseases, where complications may occur or be detected many years after initial infection (46, 83). The primary studies we identified demonstrated that different values were obtained for different groups of participants, which has implications for broader methodological discussions about whose preferences should be used to value health states (47, 48). This issue is particularly important for STIs because of the asymmetry between men and women in the burden associated with the complications of disease, even though both sexes acquire and transmit the infection itself.

We identified two previous systematic reviews focussing on outcomes for economic evaluations relating to chlamydia infection. Roberts et al. reviewed economic evaluation and modelling studies in this area published up to 2004 (17). Approximately half of the studies reviewed used ‘cost per case detected’ as the main outcome. This is not an appropriate base for policy decisions because these are only surrogate endpoints and do not determine the success of the intervention for chlamydia. The current review shows that the use of cost per QALY has increased markedly, possibly as a reflection of the impact of recommendations made by NICE, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and other decision-making bodies (15, 16, 84). A second review described alternative approaches to measure and value the quality of life associated with the sequelae of chlamydia and considered studies up to the end of 2011 (85). The authors concluded that it was

not possible to reach firm conclusions about the most appropriate techniques for measuring HRQL and valuing outcomes for chlamydia. The current review examines how HSUVs have been used within economic evaluations, and critically examines the primary data available to inform cost-effectiveness studies, based on a wide range of search terms.

Strengths and limitations

The main strength of this study is that it provides a comprehensive overview of economic evaluations about chlamydia infection that have reported their results in terms of cost per QALY. Another strength is the critical appraisal of the HSUVs that have been used in existing economic evaluations alongside a consideration of the wider primary evidence on HSUVs and associated methodological issues. There are also weaknesses associated with this review. Some studies were not explicit in stating that the condition under study was associated with chlamydia. Hence, reviewers had to use their judgement to determine which studies should be included and might have incorrectly included or excluded relevant publications. Another weakness relates to the different methods that have been used to value HRQL, which makes it difficult to make comparisons between studies and reach conclusions on the differences between them.

Conclusions

There is limited information about the HSUVs associated with chlamydia infection and its complications, which has implications for the robustness of economic evaluations in this area. Future economic evaluations need to be firmly rooted in our understanding of the natural history of the disease and its sequelae and fully discuss any limitations associated with the underlying evidence, to ensure that decision makers are as informed as possible and to inform future research agendas. To be in line with generic NICE guidelines for economic evaluations, future research is needed to understand preferences for the health states associated with chlamydia. We would argue that such research needs to fully engage with wider methodological debates about how we measure and value health states. The valuation of health states for chlamydia and other infectious diseases can be particularly challenging because it may not be possible to employ the methods which are generally viewed to be the most robust. For example, complications may occur many years after initial infection and cannot be aetiologically linked, which means that direct measurement of patient reported HRQL and the application of indirect valuation methods is not possible. Thus, there needs to be further exploration of the most appropriate methods of value elicitation to use in different settings, to ensure the best match of methods to the aims of the research (76). In

addition, further exploration is required around methods for valuing and combining preferences for health states of varying duration and occurring over different time horizons. Issues relating to the measurement and valuation of the impacts of stigma, and debates about whose preferences count also need to be examined in greater depth. Unless we adequately tackle the challenges associated with measuring and valuing HRQL for chlamydia and other infectious diseases, evaluating the cost-effectiveness of interventions in this area will remain problematic.

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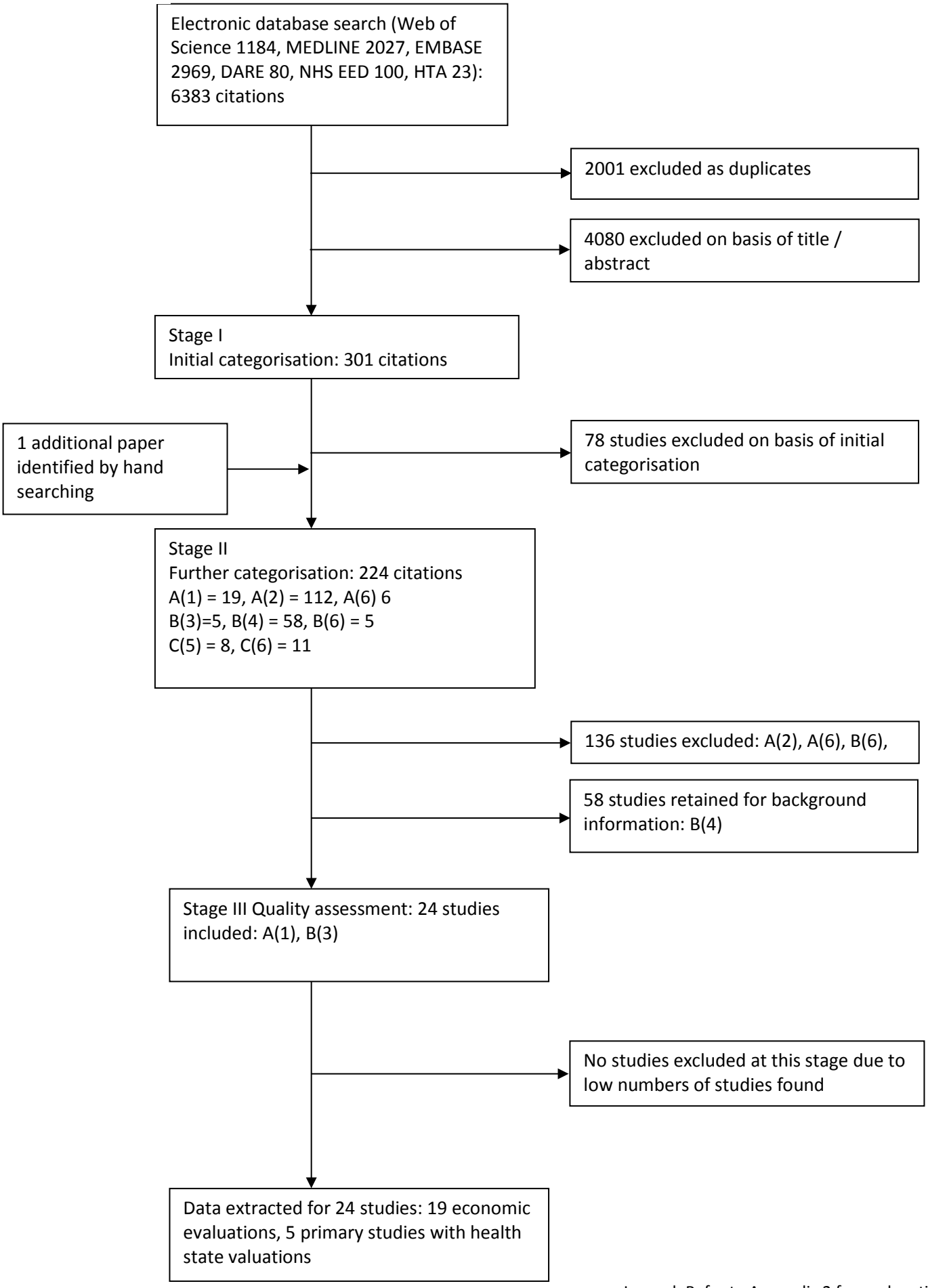
Figure 1



Legend: Refer to Appendix 2 for explanation of the categorisation criteria

Table 1: Summary of characteristics of included economic evaluations

Lead Author	Evaluation aims	Outcomes		Perspective	Population targeted by intervention and comparator	Health states included (for HSUVs)	Information presented about utility values, including source, participants, methods	Sensitivity analysis	Source for HSUVs
		QALY	MOA						
Adams (56)	Estimate the cost-effectiveness of the National Chlamydia Screening Strategy and its alternatives in England.	✓	✓	Healthcare	Men and women	Epididymitis, PID, EP, TFI, NConj, NPneum	Source cited. Authors mention the lack of information available on utilities	Probabilistic multivariate sensitivity analysis	(73)
Aledort (57)	Examine the cost-effectiveness of gonorrhoea screening in urban emergency departments.	✓	✓	Societal	Women	CPP, TFI, EP	Source and Tool cited.	Duration & weights varied in sensitivity analysis	(73)
Burgos (55)	Evaluate the cost-effectiveness of a behavioural intervention among female sex workers in Mexico.	✓	✓	Healthcare	High risk women	STI, HIV +/-STIs	Authors created their own variable to modify HRQL according to CD4+ counts.	One, two and multi-way sensitivity analyses	Unclear
de Vries (58)	Estimate the cost- effectiveness of repeated screening for *Chlamydia trachomatis* at various time intervals compared with one-off screening.	✓	✓	Societal	Men and women		Tool and source cited.	Not reported	(73)
Deogan (66)*	Assess the cost-effectiveness of a community-based intervention to provide information, and increase the availability of testing, treatment and contact tracing.	✓	✓	Societal	Men and women	Infection +symptoms, epididymitis, PID, EP, TFI, CPP, NConj, NPneum	Source and tool cited.	Series of sensitivity analyses undertaken including duration of 10 years for sequelae.	(73)
Gift (54)*	Estimate the cost-effectiveness of screening men for chlamydia compared with alternative strategies.	✓	✓	Societal	Men and women	Infection + symptoms, epididymitis, PID, EP, CPP, TFI	Source and previous study cited.	One, two and multi-way sensitivity analyses. Sequelae rate varied in sensitivity analysis.	(60, 73, 86)
Gift (69)	Evaluate the cost-effectiveness of expedited partner therapy compared with standard partner referral for the treatment of chlamydia or gonorrhoea.	✓		Healthcare and societal	Men and women	PID & sequelae	Source cited.	Univariate and simultaneous sensitivity analyses undertaken	(71, 73)

Gillespie (59)	Estimate the cost and cost-effectiveness of opportunistic screening for *Chlamydia trachomatis* in Ireland.	✓	✓	Healthcare	Men and women	Epididymitis, PID, EP, TFI, NConj, NPneum	Source cited. Limitations of data included.	Probabilistic Sensitivity Analysis undertaken	(71, 73)
Hu (60)	Test the cost-effectiveness of proposed strategies for chlamydia screening.	✓	✓	Societal	Women	Infection, PID, EP, TFI, CPP	Source cited. Authors mention the need for further information on HRQL for PID and sequelae.	Author states that utilities were varied widely in sensitivity analysis.	(73)
Hu (61)	Understand the impacts of different assumptions about the natural history of *Chlamydia trachomatis* on the cost-effectiveness of screening strategies.	✓	✓	Societal	Women	Infection, PID, EP, TFI, CPP	Source and tool for utilities given. Authors mention limited HRQL data available on PID and sequelae.	Author states that a one way senitivity analysis was undertaken on all key variables.	(73)
Shepherd (65)	Examine the effectiveness and cost-effectiveness of schools-based skills building behavioural interventions.	✓	✓	Healthcare	Men and women	Epididymitis, PID, EP, TFI, CPP	Sources, participants, methods used to generate utilities given and lack of information about HRQL for STIs discussed.	QALY losses per STI case and for complications varied in sensitivity analysis	(60, 71)
Smith (52)	Consideration of the effect of time from STI acquisition to PID development on the cost-effectiveness of different screening intervals.	✓	✓	Societal	High risk women	Infection, PID, PID complications	Sources given for utilities.	One way and multiway sensitivity analyses	(73)
Smith (64)	Examine the impact of anti-biotic costs on cost-effectiveness of PID therapy for mild to moderate PID.	✓		Societal	Women	PID, EP, ruptured EP, TOA, TFI, CPP	Source and tool used to generate utilities given.	Utility values varied over a broad range in sensitivity analyses.	(73)
Smith (63)	Estimate the cost-effectiveness of hospitalisation compared with outpatient therapy for mild to moderate PID.	✓	✓	Societal	Women	PID, EP, ruptured EP, TOA, TFI, CPP	Source, tool and participants cited.	One way and probabilistic sensitivity analyses	(73)
Sonnenberg (70)	Comparison of the cost-effectiveness of 13 methods of	✓		Societal	Women	PID, EP	Some information about methods used to elicit	Sensitivity analysis, including omitting quality of	Own values

	contraception to no use of contraception.						utilities using a convenience sample. Methods discussed in relation to study limitations.	life adjustment	
Tuite (67)	Estimate the burden of disease and costs of genital *Chlamydia trachomatis* infection in Canada	✓	✓	Societal	Men and women	Epididymitis, PID, PID complications	Some information provided on sources and participants. Lack of data mentioned.	Deterministic one way sensitivity analysis and simultaneous simulation	(71)
Walleser (62)	Examine the cost-effectiveness of a hypothetical opportunistic annual screening programme for chlamydia, compared with no screening.	✓		Healthcare	Women	PID, EP, TFI, CPP	Source and tool cited.	One and multi-way sensitivity analyses.	(73)
Wilson (53)	Conduct an analysis of the costs of testing female sex workers vs. the benefits of averting transmission of STIs to clients.	✓	✓	Healthcare	High risk men	Infection + complications	Expected value analysis undertaken to calculate utility loss for STIs	Not reported	Own values
Yeh (68)	Estimate a range for the average life-time cost of PID and its major complications.	✓	✓	Societal	Women	TFI, CPP	Details of source given and limitations in data mentioned.	Author states that utility values varied widely in sensitivity analysis, state that there is a lack of evidence for such values	(73)

MOA, major outcome averted; CPP, chronic pelvic pain; EP, ectopic pregnancy; NConj, neonatal conjunctivitis; NPneum, neonatal pneumonia; PID, pelvic inflammatory disease; STI, sexually transmitted infection; TOA, tubo-ovarian abscess; TFI, tubal factor, infertility.

* included different states for PID, EP treatment options.

Table 2: Summary of utility values included in economic evaluations, for selected health states

Lead author	Pelvic Inflammatory Disease (PID)			Chronic Pelvic Pain			Ectopic Pregnancy			Tubal Infertility		
	HSUV	Dur.	Incid.	HSUV	Dur.	Incid.	HSUV	Dur.	Incid.	HSUV	Dur.	Incid.
Aledort (57)				0.6	10 years	0.18	1	1-2 weeks	0.08	0.82	10 years	0.2
Deogan (66)	OP: 0.63 IP: 0.57	IP: 10 days OP: 2 days	0.84[a] 0.16 [a]	0.6	30 years	0.165[a]	0.58	4 weeks	0.06 [a]	0.82	30 years	0.205 [a]
Gift (54)	OP: 0.66 IPS:0.79 IPNS: 0.81	10 days 12 days 12 days	0.34[a] 0.0188[a] 0.0412[a]	0.64	5 years	0.18[a]	OP: 0.62 IP: 0.64	OP: 28 days IP: 31 days	OP:0.0510[a] IP: 0.009[a]	0.84	10 years	0.05
Gillsepie (59)	0.992		0.1							0.871	Model run for 10 years	0.108[gh]
Hu (60)	0.65	11 days	0.4[a]	0.6	5 years	0.18[a]	0.58	4 weeks	0.09[a]	0.82 [i]	Until age 50	0.2 (0.10-0.23)
Hu (61)	0.65	11 days	0.4[a]	0.6	5 years	0.12[c]	0.58	4 weeks	0.04[c]	0.82 [i]	Until age 50	0.09
Shepherd (65)	0.9	11 days	0.037[b]	0.69	5 years	0.019[b]	0.79	4 weeks	0.027 [b]	0.76	15 years	0.067 [b]
Smith (52)	0.65		0.028 [b]									
Smith (64)	0.63		0.032[j]	0.6		0.073[c]	0.58		0.01 [c]	0.82		0.028 [c]
Smith (63)	OP: 0.63 IP: 0.57		0.032[j]	0.6		0.073[c]	0.58		0.01 [c]	0.82		0.028 [c]
Sonnenberg (70)	0.91667		0.01				0.91667		0.005			
Tuite (67)	AT: 0.87 IP: 0.84	10 days 2 days	0.4 0.08	0.79	Remaining lifetime	0.18	0.87	4 weeks	0.09	0.84[f]	Remaining lifetime	0.05
Walleser (62)	0.65	11 days	0.1[b]	0.6	5 years	0.03 [a]	0.58	4 weeks	0.012 [a]	0.82	Until successful IVF / 5 years	0.01 [a]
Yeh (68)				0.6	2 years	0.181				0.82	10 years	0.205

a=applied to PID
b= applied to positive cases of chlamydia infection

c= varied for no. episodes of acute PID
d= applied to asymptomatic PID
e=applied to post pid health state
f= applied to women with infertility workup
g= applied to symptomatic PID
h= excludes patients with EP
i= Infertility QALY only applied to 0.25 who receive an infertility work up
j = recurrent PID.
Dur. = Duration
Incid. = Incidence
IP = inpatient
IPS = Inpatient surgical
IPNS = inpatient non-surgical
OP = outpatient
Ranges are not shown.

Table 3: Included primary studies with utility values

Lead author	Study Aims	Participants	Number of participants	Techniques used	Health states valued	Direct / indirect valuation	Further information on methods
Kuppermann (74)	Assess the impact of abnormal uterine bleeding and pelvic pain and pressure on HRQL and sexual functioning	Women seeking care for non-cancerous pelvic problems (aged 31-54)	By symptoms: Pain only = 272 Pain & bleeding = 278 Heavy bleeding without leiomyomata = 190 Heavy bleeding with leiomyomata = 570 Fibroids with pressure = 183	TTO	Pelvic pain, Pain & bleeding, Heavy bleeding with / without leiomyomata, Fibroids with pressure	Direct	In an interview setting, patients asked how many years of their remaining lives they would be willing to give up to live without the symptoms they were experiencing.
Smith (71)	Measure quality of life utilities for health states associated with PID	Women with / without a history of PID (aged 18+)	By disease history: PID: 56 No PID: 150	TTO; VAS	PID OP, PID IP, Ectopic pregnancy, Infertility, Chronic pelvic pain	Direct	Participants read scenarios to describe health states and then used a computerised tool to give VAS and TTO valuations for health states using time trade off methods. Subjects were asked to trade-off between living 10 years in the health state and varying amounts of time in full health.
Songer (75**)**	Identify the value that women with PID assign to health impact of future infertility	Women with signs and symptoms of PID	By pregnancy history: 0 live births = 205 1 live birth = 168 2 live births = 90 3 or more = 68	Other*	Infertility	Direct	Women with PID were asked to rate whether life with infertility was more or less meaningful than life with a series of 7 chronic conditions.
Institute of Medicine (73)	Develop a quantitative model to prioritize the development of vaccines for infectious diseases	Experts & members of committee	Expert committee members	Other	Acute urethral syndrome, cervicitis / bartholinitis, PID OP, PID IPNS, IPS, OPAIP, Ectopic pregnancy (IP/OP), Infertility, Chronic pelvic pain, Reiters syndrome, Arthritis,	Indirect	A Committee to Study Priorities for Vaccine Development developed scenarios for health conditions with input from experts. These scenarios were used to complete HUI-2 tool, which enabled utilities to be calculated.

					Urethritis, Epididymitis (OP/IP)		
Trent (72)	Investigate and compare adolescent and parent PID-related health utilities	Adolescents (aged 12-19) & their 'parents' (aged 18+)	By category: Adolescents: 134 Parents: 121	TTO; VAS	PID OP, PID IP, Ectopic pregnancy, Infertility, Chronic pelvic pain	Direct	Adolescent girls and parents completed a web based survey where they were asked to trade-off between a longer life with a health condition (described in a scenario) and a shorter life in perfect health.

PID = Pelvic Inflammatory Disease; SG = Standard Gamble; TTO = Time Trade Off; VAS = Visual Analogue Scale.

A glossary of the instruments / techniques cited which measure and value health related quality of life is provided in Appendix 3.

*Songer et al. used a quasi-rating scale preference measure using paired comparisons to obtain the value participants assigned to future fertility.

Table 4: Utility values provided by primary studies

Health state	Lead author	Result	Duration	Further information about the health states valued
Pelvic Inflammatory Disease (PID)	Institute of Medicine	HUI value Outpatient only:0.63 Inpatient – no surgery : 0.57 Inpatient - surgery: 0.46 Outpatient after inpatient: 0.83	Utilities were calculated using HUI-2	PID outpatient treatment was assumed to last for 10 days, and inpatient treatment for 2 days.
	Smith	Outpatient treatment TTO mean value (SD) • Women with PID: 0.90 (0.22) • Women without PID: 0.87 (0.26) Inpatient treatment TTO mean value (SD) • Women with PID: 0.82 (0.29) Women without PID: 0.84 (0.27)	10 year time horizon for all states	The outpatient scenario involved a 25 year old woman with pain for about 7 days (affecting usual activities) and antibiotic treatment for 14 days. It is stated that the woman has a very small chance of developing complications and a chance of getting PID again in the future. The inpatient scenario involved a hospital stay for 2-3 days with antibiotics by vein and antibiotic pills for a further 11-12 days at home. It is explained that complications are more likely when the illness requires hospital treatment.
	Trent	Outpatient treatment TTO mean value (SD) • Parents: 0.90 (0.27) • Adolescents: 0.82 (0.33) Inpatient treatment TTO mean value (SD) • Parents: 0.88 (0.30) • Adolescents: 0.78 (0.36)	50 year time horizon for all states	Scenario involved a 15 year old girl with an adapted version of the approach adopted by Smith and colleagues (71).
Chronic Pelvic Pain	Kuppermann (74)	TTO mean value (SD) • Pain only: 0.83 (0.01) • Pain & bleeding: 0.78 (0.02)	Full remaining life	72.5% women seeking care for non-cancerous pelvic problems experienced pain, 71% experienced bleeding.
	Smith (71)	TTO mean value (SD) • Women with PID: 0.69 (0.37) • Women without PID: 0.79 (0.29)	10 year time horizon for all states	Scenario used to value health states involved a 25 year old woman with pain that may slowly go away or could stay the same.
	Institute of Medicine (73)	HUI value 0.60	Utilities were calculated using HU-I2	Consequences of PID assumed to have a 5 year lag from infection. Chronic pelvic pain assumed to last for remaining life time and affect 3% infected women.
	Trent (72)	TTO mean value (SD) • Parents: 0.85 (0.31) • Adolescents: 0.76 (0.38)	50 year time horizon for all states	Scenario involved a 15 year old girl with an adapted version of the approach adopted by Smith and colleagues (71).
Tubal infertility	Smith (71)	TTO mean value (SD) • Women with PID : 0.76 (0.34) • Women without PID: 0.84 (0.29)	10 year time horizon for all states	Scenario involves a 25 year old woman who has been trying to get pregnant for one year but has been unable to do so.

	Songer (75)	% rating infertility as worse than: Sinus congestion • All women: 48 • Women with no children: 76 Chronic headache • All women: 65 • Women with no children: 62 Paralysis • All women: 12 • Women with no children: 18	Scenario suggests that infertility would last for remaining lifetime	All the women were had signs and symptoms of PID. They were asked to give their own preferences for infertility compared with other health states. Infertility defined as 'you would not be able to become pregnant or bear children'.
	Institute of Medicine (73)	HUI value 0.82	Utilities were calculated using HUI-2	Consequences of PID assumed to have a 5 year lag from infection. Tubal infertility assumed to last for remaining life time and affect 3.3% infected women.
	Trent (72)	TTO mean value (SD) • Parents: 0.91 (0.25) • Adolescents: 0.84 (0.32)	50 year time horizon for all states	Scenario involved a 25 year old woman with an adapted version of the approach adopted by Smith and colleagues (61).
Ectopic pregnancy	Smith (71)	TTO mean value (SD) • Women with PID: 0.79 (0.34) • Women without PID: 0.87 (0.26)	10 year time horizon for all states	Scenario involved 25 year old woman with an ectopic pregnancy requiring a range of treatment options. She was described as experiencing pain and possibly needing an operation but it was stated that life would return to normal in a few weeks.
	Institute of Medicine (73)	HUI value • 0.58 (outpatient only) • 0.23 (inpatient) + • 0.66 (outpatient after inpatient)	Utilities were calculated using HUI-2	All consequences of PID assumed to have a 5 year lag from infection. Duration of 4 weeks assumed for outpatient treatment for ectopic pregnancy, 3 days for inpatient treatment.
	Trent (72)	TTO mean value (SD) • Parents: 0.91 (0.26) • Adolescents: 0.82 (0.35)	50 year time horizon for all states	Scenario involved a 15 year old girl with an adapted version of the approach adopted by Smith and colleagues (61).

PID = Pelvic Inflammatory Disease; TTO = Time Trade Off.
A glossary of the instruments / techniques cited which measure and value health related quality of life is provided in Appendix 3.
*VAS values are not reported in this table.
**Songer et al. used a quasi-rating scale preference measure using paired comparisons to obtain the value participants assigned to future fertility.

Web only

Appendix 1: Example of a search strategy - MEDLINE

#	Term
1	chlamydia.mp. or exp Chlamydia Infections/ or exp Chlamydia/ or exp Chlamydia trachomatis/
2	gonorrhea.mp. or exp Gonorrhea/
3	"pelvic inflammatory disease".mp. or exp Pelvic Inflammatory Disease/ or PID.mp
4	cervicitis.mp. or exp Uterine Cervicitis/
5	ectopic pregnancy.mp. or exp Pregnancy, Ectopic/
6	epididymitis.mp. or Epididymitis/
7	exp Pelvic Pain/ or "chronic pelvic pain".mp.
8	Infertility, Female/ or tubal infertility.mp.
9	tubal factor infertility.mp.
10	"quality of life".mp. or exp "Quality of Life"/
11	life quality.mp.
12	hql or qol or HRQL or HRQOL
13	"health status indicators".mp. or Health Status Indicators/ (18858)
14	(QALY$ or "Quality adjusted Life Year$").mp. or Quality-Adjusted Life Years/
15	Health Status/ or health state$.mp. (56390)
16	(utilit$ or health utilit$).mp.
17	disutility.mp.
18	(sf 8 or sf8 or "short form 8" or shortform 8 or sf eight or "short form eight" or "shortform eight").tw.
19	(sf 12 or sf12 or "short form 12" or shortform 12 or sf twelve or "short form twelve" or "shortform twelve").tw.
20	(sf 36 or sf36 or "short form 36" or shortform 36 or sf thirtysix or "sf thirty six" or "short form thirty six" or "short form thirtysix" or "shortform thirty six" or "shortform thirtysix").tw.
21	(sf 6d or sf6d or "short form 6d" or shortform 6d or sf six or "short form six" or "shortform six").tw.
22	hui$.mp.
23	(euro qol or euro qol or eq5d or eq 5d).mp.
24	standard gamble.mp.
25	("time trade off" or tto).mp.
26	(preference$ or valuation$).mp.
27	cost utility analysis.mp.
28	economic evaluation$.mp.
29	"costs and cost analysis"/
30	cost benefit analysis.mp. or exp Cost-Benefit Analysis/
31	"cost effectiveness analysis".mp.
32	(model$ adj3 economic).mp. or exp models, economic/
33	markov$.mp.
34	or/1-10
35	or/11-34
36	35 and 36

Web only

Appendix 2: Categorisation criteria used for economic evaluations and primary studies

Initial categorisation criteria		**Further categorisation criteria**	
A	A research study which reports on costs and outcomes for individuals with/at risk of chlamydia and/or associated health states, and includes a formal economic evaluation.	1	Economic evaluation includes outcomes expressed in terms of QALYS (cost-utility analysis / cost-effectiveness study)
B	Study contains primary data on measurement and/or valuation of HRQL for individuals with/at risk of chlamydia and / or associated health states, but does not contain an economic evaluation.	2	Economic evaluation with outcomes expressed in other units e.g. cost per complication avoided (e.g. cost-effectiveness studies)
C	Study includes information relating to the measurement and/or valuation of HRQL for individuals with/at risk of chlamydia and/ or associated health states, but does not report primary data	3	Primary study of HRQL which incorporates preference-based measurement (direct and indirect methods of utility elicitation)
D	Study may have useful information about chlamydia and sequelae but does not obviously fall into A-C above (e.g. studies on prevalence or treatment options)	4	Primary study of HRQL which includes non-preference-based measurement only (utility values for health states not elicited or presented)
E	Study is not a formal economic evaluation and does not contain information relating to HRQL for health states associated with chlamydia.	5	Study reports secondary data on preference or non-preference based HRQL or is a description of methods only – no primary data
		6	Other, e.g. analysis / discussion of policy, costs, prevalence or risk factors
		7	Study does not contain information relevant to the measurement and valuation of HRQL for chlamydia and its sequelae

Studies which were categorised as A-C were read in full and categorised further. Studies which were categorised as A1, B3 were retained and data extracted. Studies which were categorised as B4 were retained for background information.

Web only

Appendix 3: Glossary of instruments discussed for measurement and valuation of health related quality of life (HRQL)

Abbreviation	Description
SG	Standard Gamble. This technique involves the respondent making a choice between an outcome which is certain and a gamble with two uncertain outcomes, involving one outcome which is better and one which is worse than the certain outcome.
HUI-2	Health Utilities Index Mark 2. The HUI-2 has seven attributes each with 3-5 levels. It is a generic instrument designed to measure health status in general populations and a range of patient groups.
TTO	Time Trade Off. This technique involves trading off between living a longer time living in less than full health, against living a shorter time in full health.
VAS	Visual Analogue Scale. A line (usually with defined end points) upon which respondents can indicate their judgements about a particular concept.

Source: Reference (66)